Remarks

This is in response to the Non-Final Office Action mailed March 2, 2007. Applicants respectfully request reconsideration of the application.

Claims 31-47 have been withdrawn. New claims 48 and 49 have been added. Claims 4-5, 8-9, 12-13, 16-17, 20-21, and 24-25 have been amended to depend from new claim 49. Claims 18-19 and 22-23 have been amended to depend from new claim 48. After entry of the amendments, claims 1-49 are pending.

A. Restriction Requirement

In a Response filed on January 22, 2007, Applicants elected with traverse group IV. Applicants traversed the restriction on the ground that it would not be an undue burden for the Examiner to search groups IV-XII or even groups I-XII.

The Examiner withdrew the restrictions between groups IV-XII but maintained the restriction between two new groups: groups I-III and IV-XII, and indicated that the new group IV-XII is being examined.

B. Rejections under 35 U.S.C. 112

The Examiner rejected claim 1 and 26-30 under 35 U.S.C. §112, first and second paragraphs, as failing to comply with the written description requirement and as being indefinite. Applicants traverse these rejections.

The Examiner objected to the terms "others" and "all other amino acid side chains" in claim 1. Claim 1 has been amended to delete the terms "others" and "all other amino acid side chains."

The Examiner indicated that claims 26-29 improperly depend from claim 1 since they are drawn to a process of making while claim 1 is drawn to a compound. Claims 26-29 have been amended to delete the reference to "a process" and indicate that the claims are drawn to a "chiral furan amino acid" as claimed in claim 1.

The Examiner rejected claim 30 as being unclear as to whether the claim is drawn to a product-by-process or compounds. In particular, the Examiner stated that it was not clear as to what is reacted with FmocOSu in dioxane-water.

Claim 30 is amended to recite a chiral furan amino acid as claimed in claims 5, 9, 13, 17, 21, or 25 where N-Fmal-protected furan amino acid is obtained by treatment of structures 5, 9, 13, 17, 21, or 25 with FmocOSu in dioxane-water.

In view of the amendments to the claims 1 and 26-30, Applicants respectfully request that the rejections under 35 U.S.C. §112, first and second paragraph be withdrawn.

C. Rejections Under 35 U.S.C. 103(a)

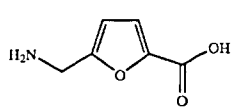
The Examiner made the following rejections under 35 U.S.C. §103(a): (i) claims 1-3, 6-7, 10-11, and 14-15 were rejected as being unpatentable over U.S. Published Patent Application No. 2005/0032707 (Prassad); (ii) claims 1-2, 6, and 10 were rejected under as being unpatentable over Chakraborty et al., Tetrahed. Lett., (2002), Vol 43(7), pages 1317-1320 (Chakraborty); and (iii) claim 1 was rejected as being unpatentable over WO 94/11398 (Wells et al.) or Hodohara et al., Nippon Kesse Shiketsu Gakkaishi (1992), Vol 3(3) pages 163-68 (Hodohara), individually. The Examiner contends that the difference between the prior art and the claimed compositions is that the rejected claims recite an alkyl at the R2 position, while the prior art teaches H at that position. The Examiner contends that H and alkyl are art recognized equivalents and, therefore, a person skilled in the art would be motivated to substitute H with alkyl. Applicants traverse these rejections.

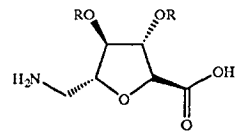
A prima facie case of obviousness based upon structural similarity requires both a showing of structural similarity and a showing that the prior art would have suggested making the specific modifications to make the claimed invention. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007)[1]. In Takeda, the Federal Circuit upheld a district court's ruling that a claim directed to a compound containing a pyridal ring with an ethyl group at the 5-position on the ring was not obvious in view of a similar compound with a methyl group at the 6-position. The defendant, Alphapharm, argued that a person skilled in the art would have selected the 6-methyl compound as a lead compound and modified that compound by (i) homologation, i.e., replacing methyl with ethyl, and (ii) moving the ethyl substituent to

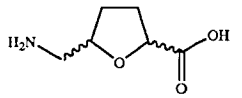
[1] A copy of this case is attached as a courtesy to the Examiner (Attachment A).

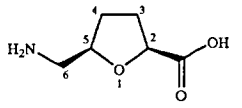
another position on the ring. The Federal Circuit upheld the district court's finding that the claims were not obvious because (i) the prior art as a whole did not demonstrate that a person skilled in the art would select the 6-methyl compound as a lead component, and (ii) there was nothing in the prior art to suggest making the specific modifications to the 6-methyl compound to achieve the claimed compound. (See 83 U.S.P.Q.2d at 1174-1177.)

At the least, there is nothing the in the prior art references to suggest modifying a 5-aminomethyl-2-furan carboxylic acid at the 6-position to provide a chiral furn amino acid. Prassad is directed to anticancer peptides that incorporate furanoid sugar amino acids in the peptide chain. Prassad discloses that the furanoid sugar amino acids are selected from the following compounds:









Compounds Saa-2, -3, and –4 contain non-aromatic, heterocyclic rings and not the aromatic furan ring. In compound Saa-2, the ring is substituted at the 3 and 4 positions with OR groups and the ring is no longer aromatic in nature. Similarly, Compounds Saa-3 and -4 are not aromatic, and include an additional H at the 2 and 5 positions. Thus, Prassad teaches modifying the ring itself to provide compounds for use in its peptides. There is nothing in Prassad to teach or suggest modifying a furan amino acid by substituting alkyl for H at the 6-position to achieve the claimed compounds.

Chakraborty discloses synthesis of unsubstituted 5-(aminoethyl)-2-furancarboxylic acids, which are used to form an 18-membered cyclic oligopeptide. Cakraborty, however, does not teach or suggest that it would be desirable to provide the furan carboxylic acid with a chiral center. Further, there is nothing in Chakraborty to indicate that a person skilled in the art would have a reasonable expectation of success in making the claimed compounds. As stated in the application, while Chakraborty discloses synthesizing the unsubstituted furan amino acid from fructose, introducing a chiral center at its C6 position requires a different approach. That is, Chakraborty does not provide any guidance on how to achieve the claimed compounds ('525 application, page 3, lines 5-8). Thus, it is only through prohibited hindsight in view of Applicants disclosure that a person skilled in the art would modify Chakraborty to arrive at the claimed compounds.

Wells is directed to cyclic compounds useful as antagonists of the platelet glycoprotein IIb/IIIa complex. The cyclic compounds include a heterocyclic ring system as a linking component to form the cyclic compound. Wells discloses a 5-aminomethyl-2-furoate hydrochloride (a salt of 5-aminomethyl-2-furoic acid). (Wells, page 49, line 5 through page 50, line 10.) Wells may disclose compounds with different R or R1 groups as indicated by the print-out attached to the Office Action. Wells, however, does not teach or suggest modifying a furan at the C6 position to provide a chiral furan amino acid. Rather, the only other modification Wells may suggest is forming isomers such as the 2,4 and 3,5 isomers (See pages 50-51 and compunds II and III.) Thus, considering Wells as a whole, Wells would not lead a person skilled in the art to modify the furans in Wells to provide a furan amino acid having a chiral center at the C6 position.

Hodohara et al. discloses amidinoaphthol derivatives for use in binding adhesive proteins to platelets by blocking RGD peptide bonding sites on GPIIb-IIIa. (See Attachment B, English Abstract.) Hodohara discloses that amidinonaphthol derivatives such as nafamostat mesilate and FUT-6258 have a better inhibitory effect than gabexate mesilate, which does not have amidinonaphthol in the structure. While the nafamostat mesilate inclues a furan ring, FUT-6258 includes a benzene ring. (See Attachment B, page 165.) There is nothing in Hodohara to suggest that the C6 carbon of nafamostat mesilate should be substituted to provide a chiral center. Rather, Hodohara would motivate a person skilled in the art to modify other compounds with an

amidinonaphthol group, but there is nothing to suggest that a furan amino acid should be modified to provide a chiral center at the C6 position.

In view of the above, the claims are patentable over the cited references. First, the references fail to teach or suggest a furan amino acid with a chiral center at the C6 position and, therefore, fail to all the elements of the claims. (MPEP §2143.)

Second, the mere fact that H and an alkyl group could be considered art recognized equivalents does not provide any teaching or suggestion to make the specific molecular modification to a 5-aminomethyl-2-furancarboxylic acid to achieve the claimed compound. Considering the references as a whole, the references fail to suggest any subsitution of a 5-aminomethyl-2-furancarboxylic acid at the C6 position let alone substituting H with an alkyl group. Rather, at best, the references suggest making other modifications to the structure such as modifying the ring itself (such as by providing a non-aromatic heterocycle in Prassad), providing an isomer (not a homolog), or modifying the carboxyl group with an amidinonaphthol group (Hodohara). That is, the references do not suggest making the molecular modifications necessary to achieve the claimed invention (*See Takeda*). Consequently, claim 1 (and any claim dependent therefrom) is not obvious in view of any of Prassad, Chakraborty, Wells, or Hodohara. Applicants respectfully request that the rejections be withdrawn.

D. Allowable Subject Matter

The Examiner indicated that claims 4-5, 8-9, 12-13 and 16-25 are rejected as being dependent upon a rejected base claim but would be allowable if rewritten in independent form.

New independent claim 48 is directed to an unnatural chiral furan amino acid carrying natural amine acid side chains at the C6-position and having a structure as shown in Formula 1. Claim 48 recites that R^2 is $(OR^3)CH_2$-, $CH_3(OR^3)CH$-, $(R^3S)CH_2$-, $CH_3SCH_2CH_2$-, $(RHN)CH_2CH_2CH_2CH_2$-; $(CONH_2)CH_2$-, $(CONH_2)CH_2CH_2$-, $(CO_2R^4)CH_2$-, $(CO_2R^4)CH_2CH_2$-, Ph-, Ar-; $PhCH_2$-, $ArCH_2$-, Phenylalkyl-, arylalkyl-, (indolyl)CH_2-, or (imidazolyl)CH_2-. While the Examiner contends that claims reciting that R^2 may be alkyl are obvious over certain prior art (which Applicants have shown is not

the case), the Examiner has not rejected the claims based on any other R^2 group. Therefore, Applicants submit that an amino acid with an R^2 group chosen from those recited in claim 48 is patentable. Claims 18-19 and 22-23 have been amended to depend from new claim 48, and Applicants submit that these claims are also patentable.

The Examiner indicated that claims 4-5, 8-9, 12-13, and 16-17 were allowable. These claims recite different R^2 groups, R^1 groups, and/or stereochemistry, but each recites that R is $CF_3COOH.H$. New, independent claim 49 recites an unnatural chiral furan amino acid having a general structure 1 as shown in Formula 1, where R is $CF_3COOH.H$. Applicants submit that new claim 49 is allowable. Claims 4-5, 8-9, 12-13, and 16-17 have been amended to depend from new claim 49 and are also believed to be allowable.

Conclusion

In view of the foregoing amendment and remarks, Applicants respectfully submit that the claims are patentable over the cited references and requests issuance of a Notice of Allowance.

In the event any fees are due in connection with the filing of this document, the Commissioner is authorized to charge those fees to our Deposit Account No. 18-0988 under Attorney Docket No. **KUMAP0111US**.

Respectfully submitted,
RENNER, OTTO, BOISSELLE & SKLAR, LLP

By /Scott M. Slaby/
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Perfect 10, Inc. v.
9-10450, 2000 WL

gress believes that this places too heavy a burden on credit cards, it can grant the cards immunity (along with corresponding responsibilities), as it did for ISPs in passing the DMCA.[25]

The majority's solicitude for "credit cards . . . as the primary engine of electronic commerce," and for preserving "the vibrant and competitive free market that presently exists for the Internet," maj. op. at 7837, is understandable but misguided. It does not serve the interests of a free market, or a free society, to abet marauders who pilfer the property of law-abiding, tax-paying rights holders, and who turn consumers into recipients of stolen property. Requiring defendants to abide by their own rules, which "strictly prohibit members from servicing illegal businesses," First Am. Compl. at 6 ¶ 20, will hardly impair the operation of a "vibrant and competitive free market," any more than did the recent law prohibiting the use of credit cards for Internet gambling. *See* 31 U.S.C. § 5364.

Nor does plaintiff seek to hold the credit cards responsible for illegal activities of which they are unaware. Plaintiff claims that it has repeatedly written to defendants, "putting them on notice of more than 240 specifically identified Celebrity Porn Websites with obvious stolen content that they were supporting." First Am. Compl. at 19 ¶ 75. Plaintiff has also sent defendants "[d]eclarations from celebrities [such as Britney Spears, Christina Aguilera, Anna Kournikova and Yasmine Bleeth] stating that they have not authorized the use of their name, likeness, or identity on pornographic websites and that they do not want their images and names so used . . . ." *Id.* at 19 ¶ 77. Credit cards already have the tools to police the activities of their merchants, which is why we don't see credit card sales of illegal drugs or child pornography. According to plaintiff, "defendants inspect websites and business premises, and obtain and review merchants' bank statements, tax returns, credit reports, and a merchant's other financial information . . . ." *Id.* at 7 ¶ 26. Plaintiff is not asking for a huge change in the way credit cards do business; they ask only that defendants abide by their own rules and stop doing business with crooks. Granting plaintiff the relief it seeks would not, I am confident, be the end of Capitalism as we know it.

This is an easy case, squarely controlled by our precedent in all material respects. Fairly applying our cases to the facts alleged by Perfect 10, we should reverse the district court and give plaintiff an opportunity to prove its case through discovery and trial. In straining to escape the strictures of our caselaw, the majority draws a series of ephemeral distinctions that are neither required nor permitted; the opinion will prove to be no end of trouble.

[25] The majority finds it "anomalous" to hold credit cards liable without DMCA-compliant notice, while ISPs are immune unless they receive such a notice. Maj. op. at 7839 n.4. But there is no anomaly in treating parties that are covered by the statute differently from those that are not. Plaintiff here *did* give ample notice to the credit cards, *see* p. 7889 *infra*, and should not have its claim dismissed for failing to allege compliance with a statute that does not apply to them.

Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.

U.S. Court of Appeals
Federal Circuit

No. 06-1329

Decided June 28, 2007

PATENTS

[1] Patentability/Validity — Obviousness — Relevant prior art — In general (§ 115.0903.01)

Prima facie case of obviousness for claimed chemical compound requires showing of structural similarity between prior art compound and claimed compound, as well as showing that prior art would have suggested making specific molecular changes necessary to achieve claimed invention; this test is consistent with legal principles prohibiting rigid application of "teaching, suggestion, or motivation" test in obviousness inquiry, since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish prima facie obviousness of new compound.

[2] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§ 115.0903.03)

Infringement defendants failed to show that person of ordinary skill in art would have se-

lected prior-art "compound b" thiazolidinedione as "lead compound," or compound that would be most promising to modify, in formulating claimed TZD derivatives used as antidiabetic agents, since plaintiffs' prior patent, which disclosed test results for nine specific compounds including compound b, does not suggest to one of skill in art that those nine compounds, out of hundreds of millions of compounds covered by application, were best-performing compounds as antidiabetics, since prior art article that examined antidiabetic effects of 101 TZD compounds, including compound b, did not identify compound b as one of most effective compounds, and instead singled out that compound as causing "considerable increases in body weight and brown fat weight," since statement in prior patent characterizing compound b as "especially important" was essentially negated by disclosure of prior art article, which taught away from compound b, and since admissions by defendants' witnesses support conclusion that compound b would not have been suitable compound for "lead compound" status.

[3] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§ 115.0903.03)

Claimed thiazolidinedione derivatives used as antidiabetic agents cannot be found obvious over closest prior art compound, identified as "compound b," under "obvious to try" standard, since that standard is applicable if prior art contains finite number of identified, predictable solutions, whereas prior art in present case, rather than identifying predictable solutions for antidiabetic treatment, disclosed broad selection of compounds, any one of which could have been selected as "lead compound" for further investigation, and since compound b exhibited negative properties that would have directed person of ordinary skill in art away from that compound; nothing in prior art provided motivation to narrow possibilities for lead compound to compound b, since evidence supports finding that one of ordinary skill would have chosen as starting point one of more than 90 compounds in prior art that did not disclose existence of toxicity or side effects, rather than compound with identified adverse effects.

[4] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§ 115.0903.03)

Infringement defendants failed to show that prior art suggested making specific molecular modifications to closest prior art compound that are necessary to achieve claimed thiazolidinedione derivatives used as antidiabetic agents, since obtaining claimed compounds from closest prior art compound, identified as "compound b," requires steps of homologating methyl group of compound b, and moving resulting ethyl group to 5-position on pyridyl ring, since evidence supports finding that there was no reasonable expectation in art that adding methyl group to compound b would reduce or eliminate known toxicity of that compound, or that changing positions of substituent on pyridyl ring would result in beneficial changes, since any presumed expectation that compound b and claimed compounds would share similar properties due to their structural similarities is rebutted by evidence that claimed compounds exhibit unexpectedly superior properties over compound b in terms of toxicity, and since record does not support defendants' contention that patentee, during prosecution of prior patent, stated that making changes to pyridyl region of compound b would lead to "better toxicity" than prior art.

[5] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§ 115.0903.03)

Federal district court did not exclude prosecution history of prior patent from scope of prior art for invention of patent in suit after concluding that prosecution history was not accessible to public, and court therefore did not commit reversible error, since record shows that court considered prosecution history of prior patent, and even expressly considered key statement therein on which defendants relied in making their obviousness argument; thus, although district court may have incorrectly implied that prosecution histories are not accessible to public, any error committed by court in this regard was harmless.

Particular patents — Chemical — Diabetes treatment

4,687,777, Meguro and Fujita, thiazolidinedione derivatives useful as antidiabetic

agents, judgment that patent obviousness affirmed.

Appeal from the U.S. Dis
Southern District of New Yo

Action by Takeda Chemi
and Takeda Pharmaceutical
Inc. against Alphapharm P
pharm Inc. for patent infr
dants appeal from decision
trial, that patent in suit is nc
ousness. Affirmed; Dyk,
separate opinion.

Related decision: 71 USF

David G. Conlin, Barbar
leen B. Carr, and Adam P.
wards Angell Palmer &
Mass.; Anthony J. Viola, c
Palmer & Dodge, New
Chao, Takeda Pharmaceutic
Inc., Lincolnshire, Ill., for p

Kevin F. Murphy, Edgar
frey A. Hovden, of From
Haug, New York, for defen

Before Lourie, Bryson,
judges.

Lourie, J.

Alphapharm Pty., Ltd. a
(collectively "Alphapharm
decision of the United St
for the Southern District of
ing a bench trial, that U.S
was not shown to be inval
§ 103. *Takeda Chem. Ind
Labs.*, 417 F.Supp.2d 341
Because we conclude tha
did not err in determinin
compounds would not ha
light of the prior art, and h
has not been shown to be

BACKGRO

Diabetes is a disease tl
by the body's inability to r
It is generally caused by i
insulin—a hormone produ
Insulin allows blood suga
is derived from food, to e
cells and be converted int
two types of diabetes, kn
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agents, judgment that patent is not invalid for obviousness affirmed.

Appeal from the U.S. District Court for the Southern District of New York, Cote, J.

Action by Takeda Chemical Industries Ltd. and Takeda Pharmaceuticals North America Inc. against Alphapharm PTY. Ltd. and Genpharm Inc. for patent infringement. Defendants appeal from decision, following bench trial, that patent in suit is not invalid for obviousness. Affirmed; Dyk, J., concurring in separate opinion.

Related decision: 71 USPQ2d 1739.

David G. Conlin, Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky, of Edwards Angell Palmer & Dodge, Boston, Mass.; Anthony J. Viola, of Edwards Angell Palmer & Dodge, New York, N.Y.; Mark Chao, Takeda Pharmaceuticals North America Inc., Lincolnshire, Ill., for plaintiffs-appellees.

Kevin F. Murphy, Edgar H. Haug, and Jeffrey A. Hovden, of Frommer Lawrence & Haug, New York, for defendants-appellants.

Before Lourie, Bryson, and Dyk, circuit judges.

Lourie, J.

Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. § 103. *Takeda Chem. Indus., Ltd. v. Mylan Labs.*, 417 F.Supp.2d 341 (S.D.N.Y. 2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

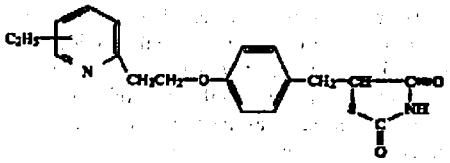
Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin—a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes—affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones ("TZDs") was introduced on the market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") first invented certain TZDs in the 1970s. Takeda's research revealed that TZDs acted as insulin sensitizers, *i.e.*, compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPAR-gamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda*, 417 F.Supp.2d at 348-49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial success since its launch in 1999. By 2003, it held 47% of the TZD market, and gross sales for that year exceeded $1.7 billion. *Id.* at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

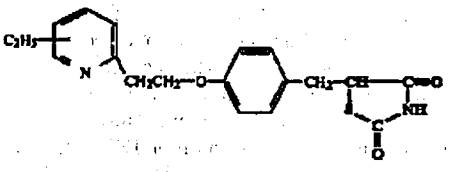
Takeda owns U.S. Patent 4,687,777 (the "'777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." '777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

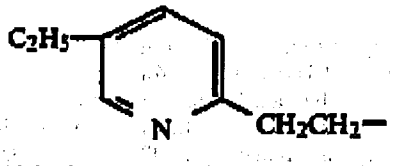
Id., claims 1 & 5.

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring.[1] That chemical structure, which has an ethyl substituent (C2H5) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda*, 417 F.Supp.2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

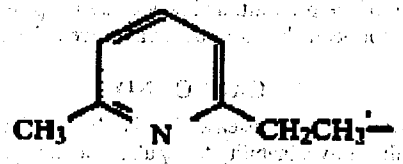
2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione.

'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:



Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to § 505(j)(2)(B)(ii), asserting that the '777 patent is invalid as obvious under 35 U.S.C. § 103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH3) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103. The court first concluded that there was no motivation in the prior art to select compound b as the lead

[1] Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." *Takeda*, 417 F.Supp.2d at 351.

on of the compound is

ric drug manufacturer, New Drug Application to the Hatch-Waxman l and Drug Administra- val under 21 U.S.C. ıufacture and sell a ge- glitazone. Alphapharm certification with its 505(j)(2)(B)(ii), assert- ıt is invalid as obvious 3. In response, Takeda ng with three other ge- ırers who also sought et generic pioglitazone, ıdants have infringed or patent.

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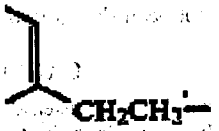

that the claimed com- been obvious over com-

found that Alphapharm ear and convincing evi- d claims were invalid as .C. § 103. The court first was no motivation in the ompound b as the lead

compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured though inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

In this appeal, we are presented with one issue, namely, whether the asserted claims of the '777 patent would have been obvious under 35 U.S.C. § 103 at the time the invention was made. An invention is not patentable, *inter alia*, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1238-39 [68 USPQ2d 1280] (Fed. Cir. 2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 [80 USPQ2d 1001] (Fed. Cir. 2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law, including our en banc decision in *In re Dillon*, 919 F.2d 688 [16 USPQ2d 1897] (Fed. Cir. 1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385] (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 [148 USPQ 459] (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law

as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. Differences Between the Prior Art and the Claims

a. election of Compound b as Lead Compound

Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

[1] We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 [226 USPQ 870] (Fed. Cir. 1985).

We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 [21 USPQ2d 1941] (Fed. Cir. 1992); *Dillon*, 919 F.2d 688 [16 USPQ2d 1897] ; *Grabiak*, 769 F.2d 729 [226 USPQ 870]; *In re Lalu*, 747 F.2d 703 [223 USPQ 1257](Fed. Cir. 1984)).

That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

We agree with Takeda and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity.[3]

[2] We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is determined, we consider that the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

[3] The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will use Alphapharm's terminology of "lead com this opinion, deciding the appeal as it has be

[4] Three divisional applications derive fro patent. Those applications matured into U 4,340,605, U.S. Patent 4,438,141, and U.S. 4,444,779 (the "'779 Patent"). The '779 p particular relevance in this appeal and is dis low. *Takeda*, 417 F.Supp.2d at 378.

Upon selecting that compound for antic research, Alphapharm asserts that one nary skill in the art would have made t vious chemical changes: first, homolc *i.e.*, replacing the methyl group with a group, which would have resulted in a compound; and second, "ring-walkir moving the ethyl substituent to anothe tion on the ring, the 5-position, thereb ing to the discovery of pioglitazone. Tl phapharm's obviousness argument cle pends on a preliminary finding that on dinary skill in the art would have compound b as a lead compound.

[2] The district court found, howe one of ordinary skill in the art would n selected compound b as the lead con In reaching its determination, the co considered Takeda's U.S. Patent 4, (the "'200 patent"), which was issued tember 1, 1981, and its prosecution The court found that the '200 pate closes hundreds of millions of TZ pounds."[4] *Takeda*, 417 F.Supp.2d at 3 patent specifically identified fifty-fo pounds, including compound b, that w thesized according to the procedu scribed in the patent, but did not disc perimental data or test results for any compounds. The prosecution histor ever, disclosed test results for nine compounds, including compound b. formation was provided to the examin sponse to a rejection in order to show claimed compounds of the '200 pat superior to the known compounds t disclosed in a cited reference. The co ever, found nothing in the '200 patent, file history, to suggest to one of ordi in the art that those nine compound the hundreds of millions of compou ered by the patent application, were performing compounds as antidiabe hence targets for modification to proved properties. *Id.* at 375.

The court next considered an art was published the following year in

Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

[2] The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's U.S. Patent 4,287,200 (the "'200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of millions of TZD compounds."[4] *Takeda*, 417 F.Supp.2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in order to show that the claimed compounds of the '200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the '779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most

been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

[4] Three divisional applications derive from the '200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the "'779 Patent"). The '779 patent is of particular relevance in this appeal and is discussed below. *Takeda*, 417 F.Supp.2d at 378.

favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda's witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that *KSR*, as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 [82 USPQ2d 1321] (Fed. Cir. 2007), mandates reversal. Relying on *KSR*, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in *Pfizer*, where we found obvious certain claims covering a particular acid-addition salt, directly supports its position.

[3] We disagree. The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on *Pfizer* fares no better. In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of this case," we found that the prior art provided "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead

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b. Choice of the C Compounds

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he *KSR* Court recognized s a design need or market roblem and there are a fi- ntified, predictable solu- dinary skill has good rea- own options within his or *KSR*, 127 S. Ct. at 1732. :s, "the fact that a combi- to try might show that it 103." *Id.* That is not the n identify predictable so- tic treatment, the prior art lection of compounds any have been selected as a further investigation. Sig- est prior art compound -methyl) exhibited nega- ould have directed one of art away from that com- se fails to present the type lated by the Court when ntion may be deemed ob- ious to try." The evidence ot obvious to try.

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compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects." Thus, *Pfizer* does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. *See Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 [81 USPQ2d 1324] (Fed. Cir. 2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

b. Choice of the Claimed Compounds

Even if Alphapharm had established that preliminary finding, and we have concluded that it did not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F.Supp.2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda's experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. *Id.*

[4] Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side effects" and thus researchers would have been inclined "to focus research efforts elsewhere." *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly from compound b in structure. *Id.* at 376 n.51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on *In re Wilder*, 563 F.2d 457 [195 USPQ 426] (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small

change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder*, our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. *Wilder*, 563 F.2d at 460.

We would note that since our *Wilder* decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," *Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of *Wilder*. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F.Supp.2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, Takeda performed additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the '779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra*, the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific

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steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.[5]

2. *Scope and Content of the Prior Art*

Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 patent prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 patent and the file history that appears in the court's opinion.

[5] We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda*, 417 F.Supp.2d at 378. In considering the prosecution history of the '779 patent, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.* The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b." *Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n.59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed. Cir. 1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the '777 patent have not been shown to have been obvious and hence invalid.

[5] The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a prima facie case of obviousness, and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

AFFIRMED

Dyk, J., concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here—claim 2—is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 ("'777 patent")—which are also referenced in the judgment—renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art U.S. Patent No. 4,287,200 ("'200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 [67 USPQ2d 1161] (Fed. Cir. 2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. *See Application of Petering*, 301 F.2d 676, 683 [133 USPQ 275] (C.C.P.A. 1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 [82 USPQ2d 1321] (Fed. Cir. 2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 [16 USPQ2d 1934] (Fed. Cir. 1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 patent, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

United States v. Martignon

U.S. Court of Appeals
Second Circuit
No. 04-5649-cr
Decided June 13, 2007

COPYRIGHTS

[1] Elements of copyright — Constitutional basis (§ 205.03)

Rights in copyright; infringement — Federal constitutional issues (§ 213.02)

Matters that could not be regulated under copyright clause of U.S. Constitution can be regulated in manner arguably inconsistent with that clause unless statute at issue is copyright law; U.S. Congress exceeds its power under commerce clause by transgressing limitations of copyright clause only if law enacted is exercise of power granted to Congress by copyright clause, and resulting law violates one or more specific limits of copyright clause.

[2] Elements of copyright — Constitutional basis (§ 205.03)

Rights in copyright; infringement — Federal constitutional issues (§ 213.02)

Infringement pleading and practice — Criminal actions (§ 217.09)

Pursuant to "textual" approach, "anti-bootlegging statute," 18 U.S.C.

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◆原 著◆

血小板接着蛋白結合部位に対する amidinonaphthol 誘導体の作用部位

—化学架橋剤を用いた検討—

程原佳子, 藤山佳秀, 井上徹也, 木藤克之,
広谷秀一, 庭川光行, 安藤 朗, 馬場忠雄,
細田四郎, 安永幸二郎

Effect of Amidinonaphthol Derivatives on the Ligand Binding Site of the Platelet Integrin Receptor GPIIb-IIIa

—Chemical cross-linking approach—

Keiko HODOHARA*1, Yoshihide FUJIYAMA*1, Tetsuya INOUE*1,
Katsuyuki KITOH*1, Shuichi HIROTANI*1, Mitsuyuki NIWAKAWA*1,
Akira ANDOH*1, Tadao BAMBA*1, Shiro HOSODA*1
and Kohjiro YASUNAGA*2

Key words: adhesive proteins, Arg-Gly-Asp, chemical cross-linking, platelet, amidinonaphthol derivatives

We have previously reported that amidinonaphthol derivatives, which have been developed as synthetic serine protease inhibitors, inhibited the binding of adhesive proteins, such as fibrinogen and fibronectin, to ADP-stimulated platelets in a competitive manner. Because this effect was similar to those of Arg-Gly-Asp (RGD) peptides, we examined the effect of amidinonaphthol derivatives on the chemical cross-linking of RGD-peptides to stimulated platelets. The radiolabeled peptides including RGD-sequence (RGDSPASSKP and KYGRGDS) were coupled to platelets by subsequent addition of chemical cross-linking agent. Platelet membrane glycoprotein IIb-IIIa (GPIIb-IIIa) became radiolabeled with the RGD peptide, and stimulation with ADP increased the extent of cross-linking. Cross-linking of the labeled peptides to ADP-stimulated platelets was inhibited by excess of nonlabeled RGD peptides, an amino acid sequence of corresponding to the carboxyl terminus of γ-chain of fibrinogen, fibrinogen and fibronectin, but not by Gly-Arg-Gly-Glu-Ser-Pro

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*2 関西医科大学第一内科〔〒 570 守口市文園町 1〕The First Department of Internal Medicine, Kansai Mesical University, Osaka, Japan. 受付:1992. 3. 5. 受理:1992. 4. 17.

Nippon Kessen Shikotsu Gakkaishi
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(GRGESP).

The cross-linking reaction was inhibited by addition of amidinonaphthol derivatives, such as nafamostat mesilate or FUT-6258, but less effectively by gabexate mesilate, which does not have amidinonaphthol in the structure. The inhibitory effect of nafamostat mesilate was dose-dependent, and 50% inhibition was obtained at the concentration of 6×10^{-5} M.

This result suggested that amidinonaphthol derivatives inhibited the binding of adhesive proteins to platelets by the blockade for RGD peptide binding sites on GPIIb-IIIa.

血小板は，活性化に伴ってその膜糖蛋白である IIb-IIa (以下 GPIIb-IIIa) に fibrinogen や fibronectin などの接着蛋白が結合し，凝集に大きな役割を果している[1]．そして，この結合においては fibronectin の接着に関与する生理活性ペプチド，Arg-Gly-Asp (RGD) を GPIIb-IIIa が確認することが知られており，この RGD は，血小板への接着蛋白結合を競合的に阻害することで，凝集を抑制する[1)2)]．

一方，われわれは合成 serine protease 阻害剤として開発された amidinonaphthol 誘導体が，先に述べた RGD と同様に fibrinogen や fibronectin といった接着蛋白の結合を抑制して凝集阻害作用を発揮することを報告した[3]．今回，この阻害作用が実際，GPIIb-IIIa での RGDS ペプタイドの結合阻害によるかどうかを，化学架橋剤を用いて検討した．

材料および方法

使用したペプタイドは，RGDS を含む10個のアミノ酸からなる fibronectin fragment, RGDSPASSKP (Sigma) と，RGD にさらに標識のために Tyr を，また化学架橋のために Lys を結合させた合成ペプタイド KYGRGDS (ペプチド研究所)で，それぞれ Bolton-Hunter 法，lactoperoxidase-glucose 法を用いて ^{125}I で標識した．Specific activity は 2～3 mCi/mg であった．

^{125}I 標識したペプタイドの血小板凝集抑制活性は，正常人の多血小板血漿 (PRP) をもちいて，ADP 凝集抑制作用で検討した．標識ペプタイドはいずれも，500 μg/ml で血小板凝集を完全に抑制した．

RGD ペプタイドの活性化血小板への結合は，D'Souza らの方法に準じて行った[4]．薬剤服用の既往のない正常人より ACD 液を用いて採血し，1,000 rpm 10分間の遠心で PRP を得，さらに遠心分離して Sepharose 2B (Pharmacia) でゲル濾過血小板を作製した．血小板は，1×10^8/ml になるよう 0.1% bovine serum albumin を含む Ca^{++}, Mg^{++} Free Tyrode's buffer に浮遊させた．このゲル濾過血小板に $CaCl_2$ を 1 mM になるよう加え，ADP 10 μM で刺激した後，標識ペプタイド 10 μM を加え，室温にて 45 分間反応させた．化学架橋剤として，PBS で溶解した 0.4 mM bis (sulfosuccinimidyl) suberate (BS^3, Pierce) を加えてさらに 10 分間反応させた後，10 mM Tris-HCl buffer (pH 7.0) で反応を停止させた．20% sucrose を用いて血小板を分離し，1% Nonidet P 40, 10 mM N-ethylmaleimide を含む PBS で溶解し，10% trichloroacetate で蛋白を抽出し，5% 2-mercaptoethanol で処理した．SDS-PAGE は，7.5% Polyacrylamide slab gel を用いて行った．ゲルは乾燥させた後，Kodak X-Omat を用いて autoradiography を行った．

阻害剤として，Arg-Gly-Asp-Ser (RGDS, 500 μM, Sigma)，fibrinogen γ-chain C 末端ペプタイドである Gly-Gln-Gln-His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val (γ 396-411, 500 μM, Sigma)，Gly-Arg-Gly-Glu-Ser-Pro (GRGESP, 500 μM, Peninsula)，fibrinogen (15 μM, Sigma)，Fibronectin (10 μM, Sigma) および合成 serine protease 阻害

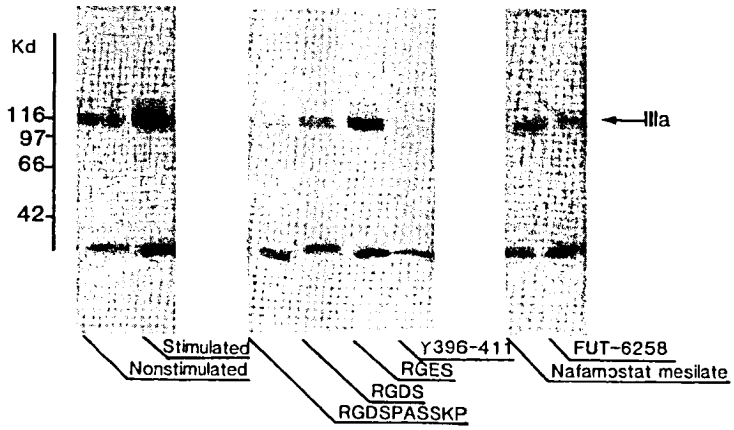
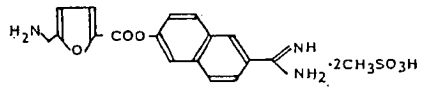
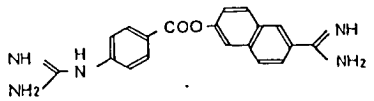


Fig. 1 Chemical cross-linking of ^{125}I-RGDSPASSKP by BS^3 to platelets. ^{125}I-RGDSPASSKP was bound to ADP-stimulated platelets for 45 minutes and then 0.4 mM BS^3 was added. The cross-linked proteins were analyzed on 7.5% polyacrylamide gels under reduced conditions. In the left panel, cross-linking was performed with non-stimulated platelets or with platelets stimulated with 10 μM ADP. In the middle panel, the specificity of the cross-linking reaction was assessed by adding 500 μM of nonlabeled peptides. In the right panel, ^{125}I-RGDSPASSKP was cross-linked to ADP-stimulated platelets in the presence of 100 μM nafamostat mesilate or 10 μM FUT-6258.

Nafamostat mesilate:



FUT-6258:



剤として，gabexate mesilate (小野薬品工業株式会社)，amidinonaphthol 誘導体である nafamostat mesilate，FUT-6258 (鳥居薬品) はおのおの生理食塩水に溶解し，ペプタイドと同時に添加した．

結　果

1. Fibronectin fragment (RGDSPASSKP) の血小板結合に対する影響

^{125}I-RGDSPASSK は，非刺激血小板においても，分子量 11 万の蛋白に結合するが，ADP で血小板を刺激することによってその結合は増強された．この結合は，非標識 RGGDSPASSKP や，RGDS，γ 396-411 で阻害されたが，非活性ペプタイドである GRGESP では阻害されなかった．

これに対して，nafamostat mesilate や FUT-6258 は，おのおの 10^{-4} M，10^{-5} M で結合を阻害した (**Fig. 1**)．

2. 合成ペプタイド KYGRGDS の血小板結合

^{125}I-KYGRGDS は，BS^3 非存在下では，ADP で活性化した血小板への結合は認められなかった．0.4 mM BS^3 の添加だけでは，血小板への結合は認められないが，カルシウム存在下にて fibronectin fragment と同様，分子量 11 万の蛋白と，さらに 14 万の蛋白へ結合が認められた．この結合は，5 mM EDTA によって阻害された (**Fig. 2**)．

3. KYGRGDS の血小板結合の特異性の検討

非標識の KYGRGDS や RGDS，γ 396-411 は，この ^{125}I-KYGRGDS の検討をほぼ完全に阻害したが，GRGESP では阻害されなかった．

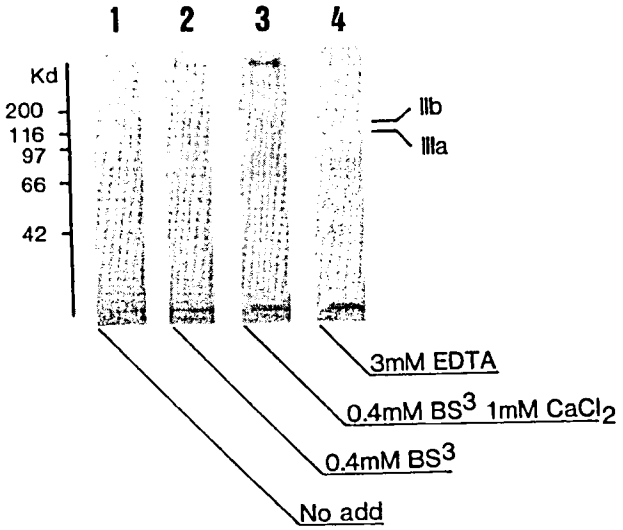


Fig. 2 Chemical cross-linking of ^{125}I-KYGRGDS by BS^3 to platelets. Chemical cross-linking of ^{125}I-KYGRGDS to ADP-stimulated platelets was carried out in the absence (lane 1) or in the presence of 0.4 mM BS^3 (lane 2～4). ^{125}I-KYGRGDS was bound to ADP-stimulated platelets in the presence of 1 mM CaCl^2 (lane 3), 5 mM EDTA (lane 4), or with no added divalent ions (lane 2). Cross-linked samples were extracted and analyzed on 7.5% acrylamide gels under reducing conditions.

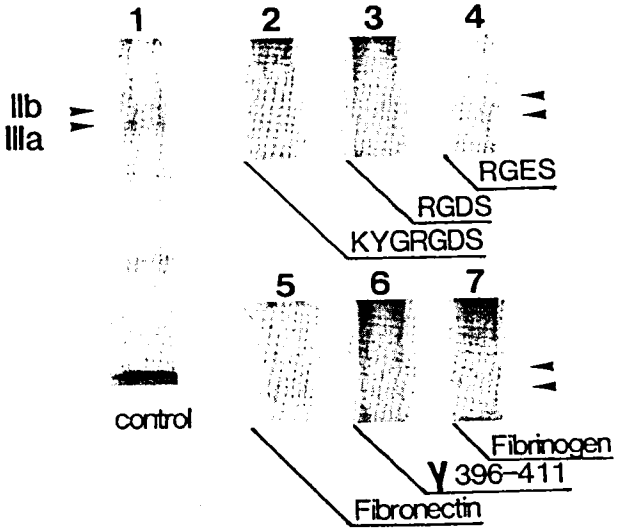


Fig. 3 Specificity of the cross-linking of ^{125}I-KYGRGDS to platelets. ^{125}I-KYGRGDS (10 μM) was cross-linked to ADP-stimulated platelets using 0.4 mM BS^3 in the absence of nonlabeled competitors (lane 1) or in the presence of 500 μM KYGRGDS (lane 2), 500 μM RGDS (lane 3), 500 μM GRGESP (lane 4), 10 μM fibronectin (lane 5), 500 μM fibrinogen related peptide (lane 6), 15 μM fibrinogen (lene 7).

また，15 μM fibrinogen でも抑制が認められたが，10 μM fibronectin による阻害は軽度であった (**Fig. 3**).

4.KYGRGDS の血小板結合に対する amidinonaphthol 誘導体の影響

ADP 刺激した血小板への KYGRGDS ペプタイドの結合は，10^{-4} M の nafamostat mesilate, 10^{-5} M の FUT-6258 で阻害されたが，gabexate mesilate ではほとんど阻害されなかった (**Fig. 4**). この nafamostat mesilate による阻害効果をデンシトメーターで解析したところ，濃度依存性であり，IC 50 は約 6×10^{-5} M であった (**Fig. 5**).

考　案

接着蛋白である fibrinogen や fibronectin, von Willebrand 因子は，その構造に RGD 配列を有しており，このペプタイドを介して接着蛋白が血小板膜上にある GPIIb-IIIa に結合する[2]. Fibrinogen の結合部位については，光架橋剤[5)6)]や化学架橋剤[4)7)]での検討がなされており，GPIIb-IIIa に結合するとされている. また，D'Souza らは化学架橋剤を用いた検討で，RGD を含む 7 個および 14 個の fibronectin fragment ペプタイドが GPIIb-IIIa，特に IIIa に強く結合することを報告し，RGD を認識する部

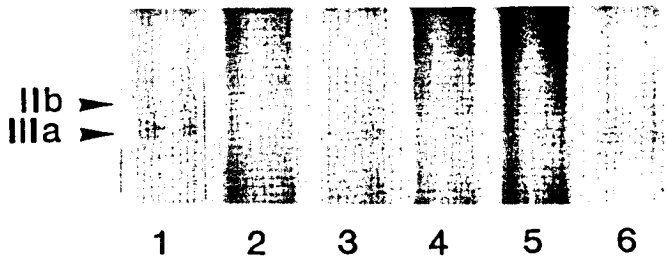


Fig. 4 Effect of amidinonaphthol derivatives on chemical cross-linking of ^{125}I-KYGRGDS to ADP-stimulated platelets. ^{125}I-KYGRGDS was bound to ADP-stimulated platelets in the absence of inhibitors (lane 1) or in the presence of 500 μM RGDS (lane 2), 500 μM GRGESP (lane 3), 100 μM nafamostat mesilate (lane 4), 10 μM FUT-6258 (lane 5) and 1 mM gabexate mesilate (lane 6).

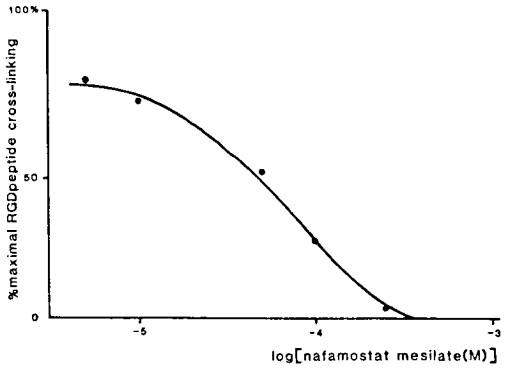


Fig. 5 Effect of nafamostat mesilate on chemical cross-linking of ^{125}I-KYGRGDS to ADP-stimulated platelets. ^{125}I-KYGRGDS was cross-linked to ADP-stimulated platelets using 0.4 mM BS^3 in the presence of 0 μM to 250 μM nafamostat mesilate. Autoradiograms of the cross-linked IIIa were analyzed by densitometer, and the data were expressed as percentage of maximal cross-linking.

位が IIIa 上にあることを示した[4]．近年，精製した GPIIIa を protease 処理し，RGD ペプタイドの結合を検討した結果，IIIa 上の# 109-171 に RGD の結合部位があることが報告されている[8]．

今回の検討でも，先の報告と同様に RGD ペプタイドは分子量 14 万および 11 万の蛋白とカルシウム依存性に結合し，これらの蛋白は GPIIb-IIIa と考えられた．特に，fibronectin fragment の架橋では IIIa への結合が強く認められた．この RGD ペプタイドの結合は，非標識のペプタイドや RGDS によって選択的に阻害されること，また，非活性ペプタイドである GRGES では阻害されなかったことから特異的であると考えられる．

一方，fibrinogen は RGD 配列を含む α-chain と γ-chain C 末端とで GPIIb-IIIa に結合する[2]．特に γ-chain C 末端のペプタイド (H 12) は fibrinogen のみならず，これらのアミノ酸配列を有さない fibronectin やvon Willebrand 因子の血小板への結合を阻害することが知られている[9]．実際，化学架橋剤を用いた検討では，H 12 は GPIIa 上の# 294-314 に結合するとされている[10]．しかし，H 12 と RGD ペプタイドの結合はお互いに競合することから，この二つのペプタイドは GPIIb-IIIa 上の立体的に近い部位に結合するものと解釈されている．今回の検討においても，fibrinogen や fibirinogen γ-chain C 末端ペプタイドは RGD ペプタイドの結合を抑制し，今までの報告に合致する結果であった．

われわれは，合成 serine proteease 阻害剤の血小板凝集抑制作用を検討するうち，amidinonaphthol 誘導体がいったん凝集した血小板の凝集を解離することや，活性化血小板への fibrinogen や fibronectin 結合を拮抗的に阻害することを見いだした[11]．このような作用

は，他の抗血小板剤では認められず，RGD ペプタイドの作用と相以しており，化学架橋剤を用いてその作用点が同一かどうか検討した．

RGDSPASSKP および KYGRGDS は，いずれもカルシウム存在下に ADP で刺激することにより GPIIIa，または IIb-IIIa と特異的に結合するが，nafamostat mesilate および FUT-6258 はこの結合を阻害した．また，同じ合成阻害剤で amidinonaphthol をその構造に有さない gabexate mesilate には，血小板凝集解離や接着蛋白結合阻害作用は認められず[11]，今回の検討でも RGD ペプタイドの結合を抑制しえなかった．

Amidinonaphthol 誘導体の血小板活性化自体に対する作用については，この薬剤が ADP による血小板凝集に対して，一次，二次凝集とも完全に抑制するが，ADP 添加時の shape change には影響しないこと[12]から，ADP による血小板活性化そのものに対する阻害作用は有していないと考えられる．

これらの結果から，amidinonaphthol 誘導体は，血小板膜 GPIIIa 上の RGD を認識する部位に直接結合するか，あるいは H 12 と同様にその近傍に作用してその conformation を変化させることにより，fibrinogen 結合を抑制し，凝集阻害作用を発揮するものと考えられた．

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